consisting of herpes virus, influenza virus, foot and mouth disease virus, hepatitis virus, vesicular stomatitis virus and rabies virus.

These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with the Examiner's position. In accordance with the requirements of 37 C.F.R. §1.121, a marked up version showing the changes to the claims, is attached herewith as Appendix A.

REMARKS

It is Applicants' understanding that the Examiner to whom the present application was previously assigned has left the Patent Office. In the interest of expediting the prosecution of this application, Applicants respectfully request an Examiner Interview after the new Examiner has reviewed this Amendment. The Examiner is requested to telephone the undersigned at (510) 337-7871 to schedule an interview.

Status of the Claims.

Claims 1-8 and 10-32 are pending with entry of this amendment, Claim 9 being canceled and Claims 16-32 being added. Claims 1-8 and 10-15 are amended. Support for the amendments to Claims 1-15 is found in the specification at least at page 34, lines 4-23. Additional support for the amendment to Claim 4 is found at least at page 2, lines 20-22. Support for Claims 18, 19, and 20 is found at least in Claims 11, 12, and 15, respectively. Claims 21 and 22 find support in the specification at least a page 2, lines 20-22. Claims 23-25 find support in the specification at page 24, line 10 through page 25, line 9. This passage also supports Claims 26-29, when taken with Claims 11 and 12. Claim 30 finds support generally throughout the specification (see, e.g., page 25, lines 11-17). Claims 31 and 32 find support at least at page 1, lines 24-28, taken with, e.g., page 6, lines 19-21and page 34, lines 4-10. Accordingly, these amendments introduce no new matter.

In the Advisory Action, the Examiner indicated that the Amendment filed on April 11, 2001 could not be entered because of, *inter alia*, confusion regarding claim number. The Examiner noted that Claims 1-9 had been canceled in Paper No. 6, yet the April 11 Amendment indicated that Claims 1-9 were pending. The apparent discrepancy arises from the renumbering of claims in the Notice of Allowance dated April 22, 1999, which was later vacated. More specifically,

the Notice of Allowance indicated that Claims 10-24 were renumbered as Claims 1-4, 10-15, and 5-9, respectively. As the Examiner requested, Applicants provide below a table showing the correspondence of the present claims with those pending in the application prior to receipt of the Notice of Allowance.

Present Claim No.	Former Claim No.
1	10
2	11
3	12
4	13
5	20
6	21
7	22
8	23
9	24
10	14
11	15
12	16
13	17
14	18
15	19

Applicants appreciate the Examiner's allowance of Claims 2, 6-8, 14, and 15. Applicants believe that the above amendments do not affect the allowability of these claims. The allowed claims were amended to ensure proper antecedent basis and consistent use of terminology throughout the claims, and the amendments are thus merely editorial in nature.

Request for Examination Under § 1.129.

37 C.F.R. § 1.129(a) states:

> An applicant in an application, other than for reissue or a design patent, that has been pending for at least two years as of June 8, 1995, taking into account any reference made in such application to any

> earlier filed application under 35 U.S.C. 120, 121 and 365(c), is entitled to have a first submission entered and considered on the merits after final rejection under the following circumstances: The Office will consider such a submission, if the first submission and the fee set forth in Sec. 1.17(r) are filed prior to the filing of an appeal brief and prior to abandonment of the application. The finality of the final rejection is automatically withdrawn upon the timely filing of the submission and payment of the fee set forth in Sec. 1.17(r). If a subsequent final rejection is made in the application, applicant is entitled to have a second submission entered and considered on the merits after the subsequent final rejection under the following circumstances: The Office will consider such a submission, if the second submission and a second fee set forth in Sec. 1.17(r) are filed prior to the filing of an appeal brief and prior to abandonment of the application.

The present application qualifies for treatment under 37 C.F.R. § 1.129 because it was pending for at least two years as of June 8, 1995, given that the application claims priority to U.S. Application No. 06/572,917, which was filed on August 30, 1983. No submissions under § 1.129 have previously been filed. The Patent Office issued a Final Office Action on September 11, 2000. A Notice of Appeal, including a petition for a 1-month extension of time, was filed on January 11, 2001 and received by the Patent Office on January 16, 2001, thereby extending the period for response to March 16, 2001. On April 11, 2001, Applicants filed a petition for a 1-month extension of time, thereby extending the period for filing an Appeal Brief to April 16, 2001. The present submission is accompanied by a petition for an additional 4-month extension, which extends the period for filing an Appeal Brief to August 16, 2001. Therefore this submission is filed "prior to the filing of an appeal brief and prior to abandonment of the application." This submission also includes the fee set forth in 37 C.F.R. 1.17(r). Accordingly, withdrawal of the finality of the Office Action and entry and consideration of this submission are proper under 37 C.F.R. 1.129(a) and are respectfully requested.

The Invention

The invention includes methods and compositions relating to a truncated, membrane-free derivative of a normally membrane-bound polypeptide, which is characterized by a membrane-binding domain and antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen. As recited in Claim 1, the derivative "is devoid of the membrane-binding

domain," but still "has exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by the pathogen." As stated in the specification:

> The success of this invention in demonstrating that a truncated form of a membrane bound protein, lacking that part of the hydrophobic-hydrophilic carboxy-terminal region responsible for binding it to the membrane, can yet be immunogenic indicates that similar results can be expected with other immunogenic membrane bound proteins, thus providing an improved source of vaccine against viruses, parasites and other pathogenic organisms.

Applicants' specification, at page 34, lines 4-10. As those of skill in the art would have readily appreciated, truncated forms of pathogen proteins that can be conveniently produced and yet are capable of eliciting antibodies have other applications, such as for use as an immunogen to produce antibodies for diagnostic assays. Those of skill in the art would also have appreciated that such truncated proteins could also be employed as standards in such diagnostic assays.

Importantly, the invention relates to "a truncated, membrane-free derivative of a polypeptide comprising a membrane-binding domain and antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen," as recited in Claim 1. Applicants discovered that, surprisingly, the deletion of the membrane-binding domain did not abolish the ability of the derivative to elicit antibodies that bind to the native protein. Even more surprising, as demonstrated with the herpes glycoprotein gD, these antibodies were shown to neutralize infectivity of the pathogen. Claim 1 relates to an immunogenic composition comprising such a truncated, membrane-free derivative. Claim 10 relates to a method of producing such an immunogenic composition and incorporates all of the elements of Claim 1 by reference to the immunogenic composition recited in Claim 1. Claim 23 relates to a nucleic acid encoding a truncated, membrane-free derivative identical to that recited in Claim 1, and Claims 26 and 27 relate, respectively, to a vector comprising this nucleic acid and a host cell comprising the vector. Claim 30 relates to a method of producing an immunogenic composition that entails "culturing the host cell of Claim 27; and . . . recovering the derivative from the culture." Claims 31 and 32 incorporate all of the elements of Claim 1. All of the other pending claims depend from one of these claims. Thus, all of the pending claims either recite or incorporate by reference the important feature of the invention described above, namely:

> An immunogenic composition comprising a truncated, membrane-free derivative of a polypeptide comprising a membrane-binding domain

> and antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen, ***wherein said derivative:***
>
> ***(a) is devoid of the membrane-binding domain*** whereby the derivative is free of membrane, ***and***
>
> ***(b) has exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by the pathogen*** . . .
>
> .

See Claim 1 (emphasis added). Accordingly, it is believed that the pending claims are commensurate with Applicants' contribution to the art.

Applicants also established that the truncated derivative of a pathogen protein could be expressed in a stable eukaryotic cell line, such as, a mammalian cell line, and recovered from the cell culture medium. This secreted derivative of the pathogen protein unexpectedly retained the capability of eliciting antibodies that bind to the native protein and neutralize infectivity of the pathogen. These features of the invention are recited in Claims 11 and 12, relating to production methods; Claims 18 and 19, relating to immunogenic compositions; and Claims 27-29, relating to vectors.

35 U.S.C. §112, First Paragraph.

Claims 1, 3-5 and 9-13 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Office Action, at 2. The rejection is respectfully traversed.

In support of the rejection, the Examiner stated:

> The claims are broadly drawn to a vaccine and a method of making a vaccine against any pathogen or to a method of immunizing a patient against herpes by administering a truncated membrane free derivative of a membrane bound polypeptide.

Office Action, at 2. This statement does not apply to the amended claims, which relate to an immunogenic composition. Furthermore, none of the previously pending claims, nor any of the amended claims, recites a method of immunizing a patient against herpes.

The Examiner also alleged that "the specification does not contain sufficient guidance or teaching to enable a vaccine against herpes by administering a truncated, membrane free derivative of a membrane bound polypeptide other than glycoprotein D. Although Applicants disagree with the Examiner for the reasons expressed repeatedly throughout the long prosecution of this application, the point is now moot, as the claims recite an immunogenic composition and a

related nucleic acid, vector, and host cell, and production methods. Thus, the Examiners' statement that "the role of the gC, gF or other glycoproteins ingenerating protective immune responses has not been clearly defined" is irrelevant to the claimed invention, as are the Examiner's comments relating to alleged difficulties with using a mouse model to identify proteins or peptides that are presumed to be improtant for inducing immunity to HSV. Office Action, at 3.

At page 3 of the Office Action, the Examiner suggested that the previously presented arguments were not congruent with the claims, stating that "the claims are not drawn to immunogenic compositions, but recite vaccines." This purported defect has been overcome by amending the claims to relate to immunogenic compositions and related compositions and methods.

The Examiner apparently viewed the Rose Declaration, filed by Applicants, as corroborating his views regarding the unpredictability of producing successful vaccines of the type previously claimed. Specifically, the Examiner found support for his position in Dr. Rose's statement that "one of ordinary skill in the art could not have predicted that a successful vaccine that raises neutralizing antibodies could have been produced based essentially on a truncated, membrane free derivative of a membrane-bound glycoprotein of the virus." Office Action, at 4. This view misses the point. Dr. Rose's statement relates to the expectation in the art prior to Applicants' invention. In any event, the Examiner's point is moot in light of the amendments to the claims.

In concluding his discussion of the §112, first paragraph rejection, the Examiner summarized as follows:

> [I]t appears that one of skill in the art would not have expected the data which appears to show protection from herpes 1 or 2 employing glycoprotein D to correlate to protection from other pathogens, including herpes virus, employing other glycoproteins. Nor would one of skill in the art expect *in vitro*, mouse, and/or rabbit data to correlate to humans. The Secher declaration states that an animal needs to be protected from disease in order to support the terminology "vaccine". There is nothing of record which shows that any other glycoproteins were protective or that animals were protected from any disease other than Herpes 1 or 2.

This rationale does not support a rejection of the amended claims. Accordingly, withdrawal of the rejection is respectfully requested.

The Advisory Action.

The Advisory Action stated, as an additional reason for the refusal to enter the above amendments:

> Entry of the claims, however, would not obviate the 35 U.S.C. 112, first paragraph rejection. Although the claims have been amended to delete the term "vaccine" the claims are still drawn to a composition that acts as a vaccine i.e. a composition that raises neutralizing antibodies against pathogen challenge *in vivo*. Therefore, the prior rejection will be maintained for reasons of record.

Applicants submit that this rationale is insufficient to support an enablement rejection of the pending claims. As discussed above, the reasons of record underlying the enablement rejection have focused on the alleged unpredictability of obtaining a protective immune response by administering a truncated membrane-free derivative of ***any*** normally membrane-bound polypeptide from any pathogen. As noted above, the previous Examiner objected that "the role of the gC, gF or other glycoproteins in generating protective immune responses has not been clearly defined." Final Office Action, at 3. The above amendments eliminate this concern.

More specifically, Claim 1 recites "a truncated, membrane-free derivative of a polypeptide comprising a membrane-binding domain and antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen, wherein said derivative." Thus, the starting point for the invention is a polypeptide capable of raising neutralizing antibodies. A wide variety of such polypeptides were known at as of the priority date of the present application and standard assays for testing additional polypeptides were in general use at that time. To satisfy the § 112, Applicants' specification need only teach how to make and use a derivative of such polypeptides that are "devoid of the membrane-binding domain whereby the derivative is free of membrane, and . . . [have] exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by the pathogen." Applicants submit that one of skill in the art could, based on the guidance in the application, make and use such a derivative of such starting polypeptide. As the record is devoid of any contrary evidence, the § 112, first paragraph, rejection cannot properly be maintained. An Examiner interview to discuss this point is respectfully requested. Accordingly, the Examiner is respectfully requested to call the undersigned at the telephone number indicated below to schedule an interview.

Conclusion.

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

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Respectfully submitted,

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